Antimineralization treatment and patient-prosthesis mismatch are major determinants of the onset and incidence of structural valve degeneration in bioprosthetic heart valves

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Background: We examined the influence of multiple valve-related parameters on the onset and incidence of valve degeneration in aortic bioprostheses through detailed echocardiographic follow-up.

Methods: In 648 patients (mean age, 73.8 ± 4.9 years) receiving an aortic valve bioprosthesis, long-term clinical (mean, 7.5 ± 3.2 years) and echocardiographic (mean, 6.5 ± 3.4 years) follow-up were performed. The occurrence of signs of structural valve degeneration (stenosis type and regurgitation type) was studied through multivariate analysis, including tissue origin, design and label size of the prosthesis, effective orifice area index (EOAi), patient-prosthesis mismatch (PPM; EOAi <0.85 cm^2/m^2), and antimineralization treatment.

Results: Structural valve degeneration (SVD) was diagnosed in 12.6% of patients. In 7.6%, it was of the stenosis type (S-SVD); in 5%, it was the regurgitation type (R-SVD). The absence of antimineralization treatment is an independent predictor of SVD, S-SVD, and R-SVD. Patient-prosthesis mismatch is an independent predictor of SVD and S-SVD, but not of R-SVD. Patients receiving a nontreated valve show a freedom of SVD at 10 years follow-up of 70.1 ± 4.3% versus 90.9 ± 3.6% in patients receiving a treated valve ($P < .0001$). Patients having PPM and receiving a nontreated valve show a freedom of SVD at 10 years of follow-up of only 59.8 ± 7.0% versus 88.7 ± 3.6% in patients also having PPM but receiving a treated valve ($P < .0001$). In patients not having PPM, the corresponding values were 78.0 ± 4.3% and 92.7 ± 3.4% for nontreated versus treated valves respectively ($P = .01$).

Conclusions: Antimineralization treatment of bioprosthetic heart valves is effective and reduces the incidence of SVD significantly. Because valve type and size are determined at the moment of implantation, the surgeon carries an important responsibility in protecting the patient from valve degeneration. (J Thorac Cardiovasc Surg 2014;147:1219-24)

ACD

In a previous study, we showed that patient-prosthesis mismatch (PPM) is associated with an increased incidence of structural valve degeneration (SVD) in patients receiving a bioprosthetic aortic valve.[1] Our report on this issue was reviewed critically and it was concluded that we presented compelling evidence that the insertion of a bioprosthesis that is too small in relation to body size is harmful in the long term.[2-5] However, Yacoub and El-Hamamsy[5] pointed out in their comment that also other forms of interactions between host and valve, apart from PPM, can cause structural and functional changes. To study the interrelationship between PPM and these confounding factors in the development of SVD, it is necessary to consider a multivariate approach that has to include not only patient-related factors, but also valve-related factors such as valve design (stented or stentless), origin of the tissue used to construct the valve (porcine aortic valve or bovine pericardium), and anticalcification treatment of the valve. For example, novel strategies to mitigate valve calcification could play a role. Indeed, we know from clinical and experimental work that besides the age of the recipient, the design-related stress distribution on the device, the origin of the tissue and the type of agent used to cross-link this tissue, and the anticalcification treatment used during the preparation of the device are fundamental factors in determining the calcification potential of bioprosthetic valves.[6] To deal with the variety of these possible factors influencing valve durability, we performed a clinical study that included 8 types of bioprostheses: stented as well as stentless valve types, porcine and pericardial valves, and valves treated with antimineralization technology or not.

METHODS

Patient Population

A group of 648 patients (mean age, 73.8 ± 4.9 years; 52% males) underwent aortic valve replacement using a bioprosthetic valve. Their

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Abbreviations and Acronyms

EOA = effective orifice area
EOAi = effective orifice area index
PPM = patient-prosthesis mismatch
R-SVD = regurgitation-type structural valve degeneration
S-SVD = stenotic-type structural valve degeneration
SVD = structural valve degeneration

mean body surface area was 1.78 ± 0.19 m^2. The majority (94%, n = 609) had aortic valve stenosis combined eventually with regurgitation, and 6% (n = 39) had regurgitation exclusively. The mean ejection fraction was 62%, and 87% (n = 564) was in sinus rhythm, 8% (n = 52) in atrial fibrillation, and 5% (n = 32) had pacemaker rhythm. Five percent of the patients (n = 32) were in New York Heart Association functional class I, 48% (n = 311) in class II, 40% (n = 259) in class III, and 7% (n = 46) in class IV. Forty-nine percent of patients (n = 312) received concomitant coronary bypass grafting.

Prosthetic Valve Characteristics

Specific valve models, design, tissue origin, and tissue treatment are listed in Table 1, together with patient-related variables grouped per valve type. Two types of valve design were used: stented (n = 449 or 69% of cases) or stentless (n = 199 or 31%) bioprostheses. Median label size was 23 mm (range, 19-29 mm), for stentless valves it was 25 mm (range, 19-29 mm), and for stented valves it was 23 mm (range, 19-29 mm). Two types of biologic material were used: porcine aortic valves (n = 396 or 61%) and bovine pericardial tissue (n = 252 or 39%). The valves were either treated with an antimineralization treatment (n = 377 or 58%) or had no treatment (n = 271 or 42%).

Patient-Prosthesis Mismatch

Patient-prosthesis mismatch was calculated using the patients' body surface area and the values of the corresponding reference effective orifice area (EOA) of the used valves according to literature data.[7-9] PPM was defined as an EOA index (EOAi) <0.85 cm^2/m^2.

Follow-up and Structural Valve Deterioration

Clinical and echocardiographic follow-up was performed at hospital discharge and thereafter periodically by the referring cardiologist. Survival, reoperation, cerebrovascular accidents, bleeding complications, anticoagulation therapy, New York Heart Association class, and cardiac rhythm were recorded. In this study, echocardiographic findings during follow-up were used to detect early signs of SVD.[1] Two types of SVD were distinguished: a stenotic type (S-SVD) or a regurgitation type (R-SVD). For every valve model used, the mean value of the peak pressure gradient across the valve at discharge was determined for the patient population receiving this valve model. A cutoff value was then calculated by adding 1 standard deviation to the obtained mean value of the peak pressure gradient of this specific valve model. When, during the follow-up, persisting values of the peak pressure gradient above this cutoff occurred, the diagnosis of S-SVD was made. In none of the patients, regardless of the valve model, was a valvular regurgitation score >1/4 found at discharge. Therefore, a patient developing a valvular regurgitation of a degree >1/4 during follow-up, was diagnosed as having R-SVD. Patients developing a combination of valve stenosis and regurgitation were classified as having S-SVD. For the analysis of SVD, we obviously excluded the in-hospital deaths (n = 37) and patients with insufficient echocardiographic follow-up (n = 31), resulting in a population of 580 patients with long-term clinical and echocardiographic follow-up.

Statistical Analysis

For the formulation of valve-related complications, standard guidelines and definitions of terms were used according to recently published recommendations.[10] Univariate testing for comparisons between groups was performed using nonparametric tests (Kruskal-Wallis, Mann-Whitney, and Wilcoxon). Overall survival and freedom from SVD were visualized using Kaplan-Meier curves. Log-rank testing was used for comparison between 2 groups. Further analysis included standard single predictor and multivariable ($P < .1$ threshold to enter the model) Cox proportional hazards models. The following variables were analyzed: (1) patient-related variables such as age, gender, need for concomitant bypass grafting, treated diabetes mellitus, hypercholesterolemia, arterial hypertension, obesity (body mass index >30), statin use, and presence of metabolic syndrome (at least 3 of the previous 5 factors present); and (2) valve-related variables, including labeled size, type, design (stented or stentless), tissue origin (porcine or pericardial), presence of anticalcification treatment, EOAi, and PPM. $P < .05$ was considered statistically significant for the study.

RESULTS

Follow-up

Follow-up was 98% complete (12 patients were lost to follow-up). The median follow-up period was 7.7 years (mean, 7.5 ± 3.2 years), with a maximum of 15.6 years. Implant and follow-up periods for the different valve models are given in Table 1. Considering length of follow-up, there are no significant differences between the subgroups ($P = .15$). Echocardiography was performed in 95.3% of the hospital survivors. In total, 2990 echo reports were collected (mean, 4.6 echo reports per patient). In 61% of the patients, the last echocardiography was recorded within the last year of clinical follow-up, and in 79% was within the last 3 years. We reached a median echocardiographic follow-up of 7.0 years (mean, 6.5 ± 3.4 years).

Clinical Outcome

Hospital mortality was 5.2%. Overall survival at 10 years was 48.3 ± 4.1% and freedom from cardiac death was 73.7 ± 5.4%. At 10 years, freedom from hospital readmission for cardiac reasons was 54.6 ± 3.9%, freedom from thromboembolic events and/or major anticoagulation-related bleeding was 95.8 ± 1.7%, and freedom from reoperation was 94.4 ± 1.3%. Twenty patients developed acute bacterial endocarditis during the postoperative follow-up. These patients were excluded from further analysis of SVD.

Patient-Prosthesis Mismatch

The overall incidence of PPM was 53%. The incidence in each valve type is listed in Table 1. Forty-seven percent of the patients had an EOAi >0.85 cm^2/m^2, 49% had an EOAi between 0.85 cm^2/m^2 and 0.65 cm^2/m^2, and 4% had and EOAi <0.65 cm^2/m^2. For further analysis, we considered a value <0.85 cm^2/m^2 as PPM (53%). Stentless valves had significantly less PPM (44 patients out of 199,

or 22%) than stented valves (301 out of 449, or 67%; $P < .0001$). Patients having PPM had significantly higher peak gradients at discharge than patients not having PPM (31.1 ± 11.7 mm Hg vs 21.3 ± 8.5 mm Hg, $P < .0001$).

Structural Valve Degeneration

The diagnosis of SVD was made in 73 patients (12.6%). Forty-four patients had a stenotic valve (S-SVD; 7.6%) and 29 patients had an incompetent valve (R-SVD; 5.0%). Based on these echocardiographic criteria, freedom from SVD was substantially lower than that of reoperation (Figure 1). At 10 years, freedom from SVD was 81.0 ± 2.4% whereas freedom from reoperation was 94.4 ± 1.3%. Stringent echocardiographic follow-up leads to (early) detection of SVD in a phase when reoperation is not required (yet).

In the univariate Cox analysis toward SVD and toward the 2 subtypes (S-SVD and R-SVD), the following variables revealed a P value < .1: (1) labeled valve size, EOAi, absence of anticalcification treatment, and presence of PPM for SVD and for S-SVD; and (2) labeled valve size, tissue origin, and absence of anticalcification treatment for R-SVD. These variables were inserted into the multivariable Cox models (Table 2). None of the patient-related variables proved to be significantly related to any of the SVD forms.

The multivariable Cox analysis revealed that absence of anticalcification treatment is an independent predictor of SVD, S-SVD, and R-SVD. Patient-prosthesis mismatch is an independent predictor of SVD and S-SVD, but not of R-SVD. Table 2 summarizes all P values from the single-predictor analysis, together with the hazard ratios resulting from the multivariable Cox analysis.

Patients receiving a nontreated valve show a freedom from SVD (all forms) at 10 years of follow-up of 70.1 ± 4.3% versus 90.9 ± 3.6% in patients receiving a treated valve (Figure 2, *A*; $P < .0001$). Valve treatment induces a significant delay of both S-SVD (Figure 2, *B*) and of R-SVD (Figure 2, *C*). Stenotic-type SVD starts to occur much earlier (at about 3-5 years) than R-SVD, which starts late (at about 9-10 years), but progresses quickly in the group having a nontreated valve (Figure 2, *B* and *C*). Figure 3 illustrates the effect of PPM on S-SVD, as we have demonstrated previously.[1]

Additive Effect of Anticalcification Treatment and PPM

The interaction between PPM and anticalcification treatment on the incidence of SVD is depicted in Figure 4. Patients having PPM and receiving a nontreated valve show a freedom of SVD at 10 years of follow-up of only 59.8 ± 7.0% versus 88.7 ± 3.6% in patients having PPM but receiving a treated valve ($P < .0001$). In patients not having PPM, the corresponding values were 78.0 ± 4.3% and 92.7 ± 3.4% for nontreated versus treated valves, respectively ($P < .01$).

DISCUSSION

The efficacy of antimineralization treatments of bioprosthetic heart valves has never been proved in a clinical setting. Although several of these antimineralization treatments are actually applied to clinically available tissue valves, clinical trials to show their efficacy were never required by health care authorities. The only evidence of efficacy is provided by experimental studies, including the accelerated calcification models in sheep.[6,11-13] From clinical work, we know that the age of the recipient will determine the incidence of prosthetic valve degeneration.[14,15] Experimental work was needed to show that factors such as the design-related stress distribution on the device, the origin of the tissue, the type of agent used to cross-link this tissue, and, last, the anticalcification treatment used during the preparation of the devices are all factors determining the calcification potential of these bioprosthetic valves.[6,11-13]

In this study, we included the following valves as nontreated prostheses: the Pericarbon and the Mitroflow (both Sorin, Saluggia, Italy) valve as stented bovine pericardial valves, the Labcor valve (Sulzer Carbomedics, Austin, Tex) as a stented porcine valve, and the Toronto SPV (St Jude Medical, St Paul, Minn) and the Prima (Edwards, Irvine, Calif) valves as stentless porcine prostheses. As treated valves, we included the Perimount valve (Edwards) as a stented pericardial valve, the Mosaic valve (Medtronic, Minneapolis, Minn) as a stented porcine valve, and the Freestyle valve (Medtronic) as a stentless porcine valve. This means that we accepted alpha-oleic acid as a treatment in the Mosaic and the Freestyle valves, and Tween-80 as a treatment in the Perimount valve.[6]

Our current data suggest that antimineralization treatment of bioprosthetic heart valves is effective and reduces the onset and incidence of both forms of SVD significantly. Remarkable is that these treatments not only prevent or at least postpone prosthetic valve stenosis, but also can prevent valve regurgitation, most likely caused by cusp rupture. As Carpentier[2] highlighted in his editorial comment on our previous work, the originality of our previous study[1] relating PPM to SVD was in the distinction between 2 simple categories of valve structural deterioration (ie, S-SVD and R-SVD) and their relation to PPM. Indeed, not all bioprostheses showing SVD exhibit stenosis and calcification. Some valves show only rupture of the cusps, whereas others show the combination of leaflet calcification and rupture.[16,17] Cusp ruptures were often associated with fatigue of the material; but, on the other hand, tears in the leaflets were also associated with micro- or macroscopic calcification of the tissue, which are possible causes of cusp ruptures.[18,19] We classify bioprosthetic valves showing increasing pressure gradients

TABLE 1. Descriptive data of the valve types included in the study

Valve Type	n	Implant period	Design	Tissue origin	Treatment	Incidence PPM	Clinical FU (y)
Mosaic	148	1997-2003	Stented	Porcine	Treated	67.6%	7.1 ± 2.9
Pericarbon	48	1993-1995	Stented	Pericardial	Untreated	70.8%	7.3 ± 4.3
Perimount	165	1995-2004	Stented	Pericardial	Treated	61.8%	7.7 ± 2.0
Labcor	49	2000-2003	Stented	Porcine	Untreated	85.7%	6.0 ± 2.6
Mitroflow	39	2000-2004	Stented	Pericardial	Untreated	58.9%	6.1 ± 2.9
Toronto SPV	85	1995-2002	Stentless	Porcine	Untreated	23.5%	8.7 ± 2.9
Freestyle	64	1996-2005	Stentless	Porcine	Treated	25.0%	7.2 ± 3.1
Prima	50	1991-1993	Stentless	Porcine	Untreated	18%	9.4 ± 3.7

PPM, Patient-prosthesis mismatch; *FU*, follow-up (mean ± standard deviation); *CABG*, concomitant coronary bypass grafting; *AHT*, hypertension; *DM*, treated diabetes mellitus; *Chol*, hypercholesterolemia; *Obes*, obesity (body mass index >30); *Stat*, statin use; *MS*, presence of metabolic syndrome (at least 3 of the previous 5 factors present); *SPV*, stentless porcine valve.

across the valve in combination with regurgitation as S-SVD. Valves demonstrating only valvular regurgitation are classified as R-SVD. To make this distinction, complete echocardiographic follow-up data, including pressure gradients across the valve, description of leaflet calcification, and semiquantitative indications of regurgitation, become mandatory to classify valve failure. It is clear that, only through stringent echocardiographic follow-up, an early detection of SVD is possible during a phase when reoperation is not required (yet). Too many clinical reports studying SVD use the (late) event of reoperation as the moment of (end-stage) SVD diagnosis.

The concept of PPM implies, as a main hemodynamic consequence, the generation of higher than expected gradients through normally functioning prosthetic valves.[20] The incidence of moderate and severe PPM can vary substantially within published series, depending on valve types studied and used EOA reference values.[21] High-pressure gradients at the outflow of the left ventricle can explain the association of PPM with less regression of left ventricular hypertrophy, more cardiac events, and lower survival, as shown by Pibarot and Dumesnil.[7] However, such a disturbance of hemodynamic flow patterns might also have an influence on the structural integrity of the prosthetic valve tissue and may result in the calcifying stenosis of the prosthesis that we find in our patients having PPM. We showed clearly that PPM is an independent predictor of S-SVD but not of R-SVD. On the other hand, we also showed that absence of treatment of bioprosthetic valves predicts a greater incidence of S-SVD and R-SVD. This finding suggests that alpha-oleic acid and Tween-80 treatments protect not only against leaflet calcification, but also against leaflet matrix instability and rupture.

The clinical consequence of our findings is clear: Besides the prevention of PPM, the use of nontreated bioprosthetic heart valves should be avoided. Because valve type and size are determined at the moment of implantation, the surgeon carries an important responsibility in protecting the patient from valve degeneration.

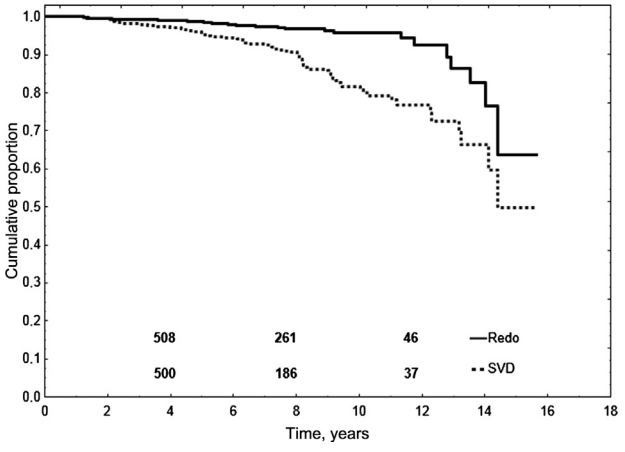

FIGURE 1. Freedom from reoperation (*solid line*) and SVD (*dashed line*). It is clear that stringent echocardiographic follow-up leads to detection of SVD in a phase when reoperation is not required (yet). Numbers at risk are shown at 4, 8, and 12 years. *SVD*, Structural valve degeneration; *Redo*, reoperation.

Study Limitations

Structural valve degeneration is a nonfatal event. Its diagnosis and the time of detection depend highly on the frequency and completeness of echocardiographic follow-up within the patient cohort. In the analysis of these events,

TABLE 2. Statistical analysis

Factor	SVD	Stenotic-type SVD	Regurgitation-type SVD
Tissue origin	—*	—*	NS†
No treatment	2.97 (2.32-3.82)	4.44 (3.16-6.23)	3.16 (2.01-4.95)
EOAi	NS†	NS†	—*
PPM	1.95 (1.52-2.51)	2.69 (1.82-3.97)	—*
Size	NS†	NS†	NS†

Multivariable analysis of SVD (all forms), stenotic-type and regurgitation-type SVD. Analyzed factors included labeled valve size, EOAi, absence of anticalcification treatment, and presence of PPM for SVD and for stenotic-type SVD; and labeled valve size, tissue origin, and absence of anticalcification treatment for regurgitation-type SVD. If the factor remained significant in the multivariable setting, the resulting hazard ratio is shown with its 95% confidence interval. *SVD*, Structural valve degeneration; *NS*, not significant; *EOAi*, effective orifice area index; *PPM*, patient-prosthesis mismatch. *The factor was not analyzed within the multivariable model given its nonsignificant univariate *P* value. †The factor was no longer significant in the multivariable model.

TABLE 1. Continued

Echo FU (y)	Male	CABG	AHT	DM	Chol	Obes	Stat	MS
6.0 ± 3.4	78 (53%)	82 (55%)	109 (74%)	21 (14%)	40 (27%)	30 (20%)	25 (17%)	16 (11%)
5.5 ± 3.8	22 (46%)	41 (83%)	32 (68%)	7 (15%)	7 (15%)	3 (6%)	3 (6%)	3 (6%)
5.6 ± 3.3	84 (51%)	72 (44%)	121 (74%)	24 (15%)	63 (39%)	24 (15%)	35 (21%)	18 (11%)
5.5 ± 2.7	28 (57%)	27 (53%)	21 (43%)	5 (10%)	19 (39%)	6 (12%)	13 (27%)	3 (6%)
6.0 ± 2.9	21 (54%)	20 (51%)	20 (51%)	5 (13%)	9 (23%)	3 (8%)	7 (18%)	1 (3%)
7.9 ± 3.1	43 (51%)	45 (52%)	38 (45%)	11 (13%)	39 (46%)	11 (13%)	22 (26%)	9 (11%)
7.0 ± 3.6	36 (56%)	25 (39%)	44 (69%)	14 (22%)	16 (25%)	14 (22%)	9 (14%)	9 (14%)
7.3 ± 3.7	25 (50%)	0 (0%)	30 (60%)	4 (8%)	9 (18%)	4 (8%)	1 (2%)	1 (2%)

ideally an interval-censored technique is used, with the time interval between the last echocardiographic follow-up demonstrating normal valve function and the first echocardiographic follow-up demonstrating SVD. In 2 previous studies, we did so and used the poor man's data augmentation multiple imputation method for interval censored data, according to Pan.[1,22,23] In addition, the nonparametric Turnbull estimate was used instead of Kaplan-Meier curves to create a graphic representation of the time to SVD. Post factum, however, no difference was shown between the outcome of these models in comparison with the regular Cox analysis and Kaplan-Meier estimates, which was most likely a result of the fact that our echocardiographic data were quite extensive and complete. In this series, even

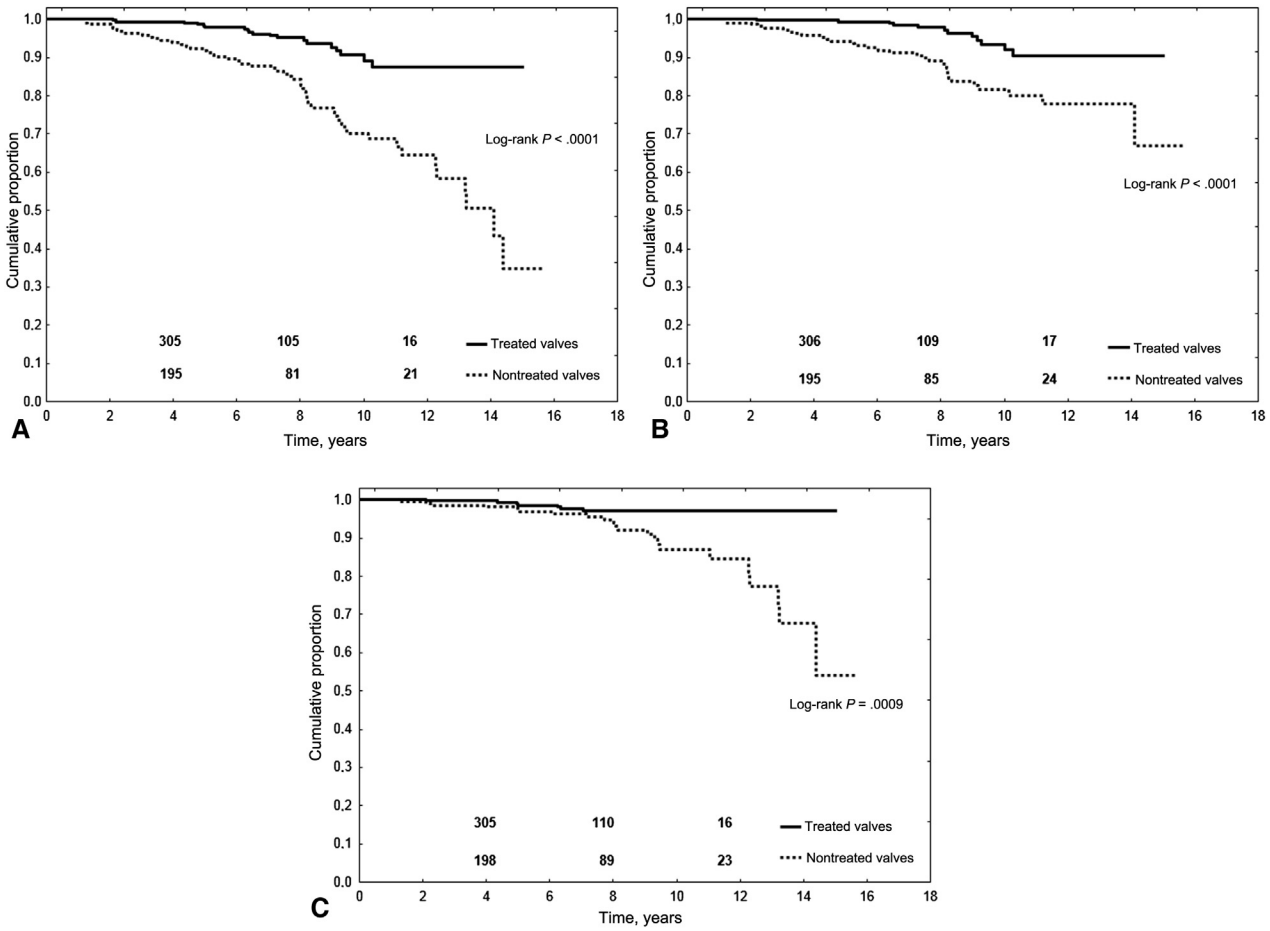

FIGURE 2. A, Freedom from SVD (all forms) in patients with a treated or a nontreated valve (log-rank $P < .0001$). B, Freedom from stenotic-type SVD in patients with a treated or a nontreated valve (log-rank $P < .0001$). C, Freedom from regurgitation-type SVD in patients with a treated or a nontreated valve (log-rank $P = .0009$). Numbers at risk are shown at 4, 8 and 12 years.

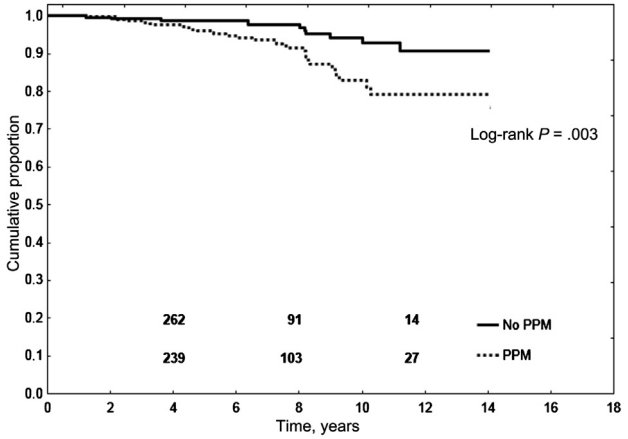

FIGURE 3. Freedom from stenotic-type SVD in patients with or without PPM (log-rank $P = .003$). Numbers at risk are shown at 4, 8, and 12 years. *PPM*, Patient-prosthesis mismatch.

more echocardiographic data were collected, which led us to refrain from these ''complex'' and less familiar models and to use regular statistical methods. Throughout this study, peak gradients were used for the SVD diagnosis, because the incompleteness of mean transvalvular gradients and EOAi's inhibited their use in the analysis. We were unable to reveal an effect of patient-related variables on SVD, potentially because of the older mean age of our population and the relative low number of SVD events, compromising the power of the analysis. The low event rate also makes it impossible to discriminate the effect of different types of antimineralization agents.

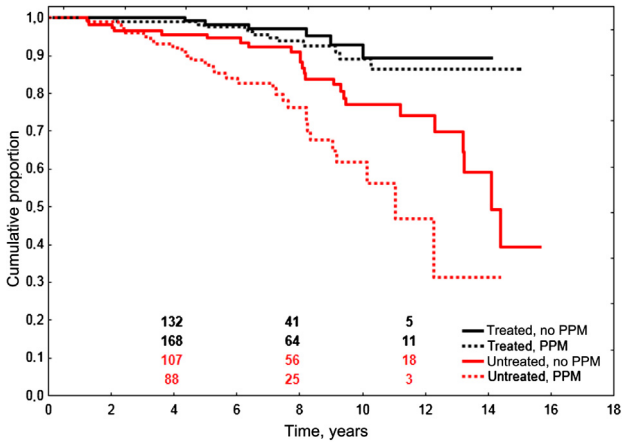

FIGURE 4. Additive effect of valve anticalcification treatment and PPM on freedom from SVD (all forms). *Black curves* represent treated valves; *red curves* represent untreated valves. Patients with PPM are represented with *dashed lines*. Patients having PPM and receiving an untreated valve show a freedom from SVD at 10 years of follow-up of only 59.8 ± 7.0% versus 88.7 ± 3.6% in patients having PPM but receiving a treated valve ($P < .0001$). In patients not having PPM, the corresponding values were 78.0 ± 4.3% and 92.7 ± 3.4% for nontreated versus treated valves, respectively ($P < .01$). Numbers at risk are shown at 4, 8, and 12 years. *PPM*, Patient-prosthesis mismatch.

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